Turnitin Originality Report

Processed on: 2020年07月21日 21:57 WIB
ID: 1360407266
Word Count: 4099
Submitted: 1

Similarity Index	Similarity by Source	
24%	Internet Sources:	23%
	Publications:	9%
	Student Papers:	13%

The Effect of Ethanol Extract Black Cumin (Nigella sativa) on Renal ET-1 and eNOS Expression Mice Preeclampsia Model By Sukesi Sukesi

7% match (Internet from 10-Jul-2019)
http://directory.indianjournals.com/ijor.aspx?target=ijor%3Aijfmt&type=eboard

4% match (Internet from 11-Jul-2020)
http://www.i-scholar.in/index.php/ijphrd/search/authors/view?firstName=Ani&lastName=Media+Harrumi&middleName=

2% match (Internet from 08-May-2019)
http://repo.unand.ac.id/19720/1/OK%20IJPHRD_November_2018%20%283%29-compressed.pdf

2% match (Internet from 10-Mar-2010)
http://www.ijfmt.com/downloadpdf/freepdf/july-dec08.pdf

2% match (Internet from 04-Nov-2019)
http://www.ejurnal-analiskesehatan.web.id/index.php/JAK/article/view/247

1% match (Internet from 16-Aug-2011)
http://www.ijfmt.com/

1% match (Internet from 31-Oct-2019)
http://repository.unair.ac.id/90039/1/Untitled3.pdf

1% match (publications)
Humaira Rahma, I.W.A. Indrawan, Mukhamad Nooryanto, Rahajeng, Kusnarman Keman. "Effect of a black cumin (Nigella sativa) ethanol extract on placental angiotensin II type 1-receptor autoantibody (AT1-AA) serum levels and endothelin-1 (ET-1) expression in a preeclampsia mouse model", Journal of Taibah University Medical Sciences, 2017

1% match (student papers from 15-Jun-2020)
Submitted to Universitas Sebelas Maret on 2020-06-15

1% match (Internet from 30-Apr-2019)
http://ijocm.org.in/editorial.html

1% match (publications)
Rubiati Hipni. "PENGARUH EKSTRAK ETANOL BIJI JINTEN HITAM (Nigella Sativa) TERHADAP EKSPRESI ET-1 AORTA PADA MENCIT MODEL PREEKLAMPSIA", Medical Laboratory Technology Journal, 2016

Volume 13 Number 4 October-December 2019 Indian Journal of Forensic Medicine & Toxicology EDITOR in Chief Prof. R K Sharma Formerly at All India Institute of Medical Sciences, New Delhi, E-mail: editor. ijfmt

@gmail.com EDITOR Prof. Dr. Adarsh Kumar Forensic Medicine& Toxicology, AIIMS, New Delhi INTERNATIONAL EDITORIAL ADVISORY BOARD 1. 2. Prof Mete Gulmen Cukurova University, TURKEY Prof. Leandro Duarte De Carvalho, Minas Gerais, Belo Horizante, Brazil 3. Prof. Donata Favretto (Full Professor) Forensic Toxicology at University of Padova, Italy 4. Prof. Babak Mostafazadeh Department of Forensic Medicine & Toxicology, Shahid Beheshti University of Medical Sciences, Tehran- Iran 5. 6. 7. Prof Halis Dokgoz, Mersin University, TURKEY Prof Jozef Sidlo, Comenius University, Bratislava, SLOVAKIA Dr. Rahul Pathak (Lecturer) Forensic Science, Dept of Life Sciences Anglia Ruskin University, Cambridge, United Kingdom 8. Dr. Hareesh (Professor & Head) Forensic Medicine, Ayder Referral Hospital, College of Health Sciences, Mekelle University, Mekelle Ethiopia East Africa 9. Dr. Mokhtar Ahmed Alhrani (Specialist) Forensic Medicine & Clinical Toxicology, Director of Forensic Medicine Unit, Attorney General's Office, Sana'a, Yemen 10. Dr. Sarathchandra Kodikara (Senior Lecturer) Forensic Medicine, Department of Forensic Medicine, Faculty of Medicine, University of Peradeniya, Sri Lanka 11. Dr Noha A. Magdie El Rafie, Forensic Toxicology, Ain Shams University, Cairo, EGYPT SCIENTIFIC COMMITTEE 1. Prof Udai Pratap Singh, Department of Anthropology Lucknow University Lucknow 2. Dr Anil Rahule (Associate Professor) Dept of Anatomy, Govt Medical College Nagpur 3. Dr Shankar Bakkanwar (Associate Professor) Forensic Medicine, Kasturba Medical College, Manipal, Karnatakad 4. 5. Dr K. Ravikumar Raksha Shakti University, Ahmedabad, Gujrat. Dr. Pragnesh Parmar (Associate Professor) Forensic Medicine, Valsad, Gujrat 6. Dr Vandana Mudda (Awati) (Associate Prof) Dept of FMT, M.R.Medical College,Gulbarga, Karnataka, 7. Dr. Asha Srivastava (Senior Scientific Officer) Forensic Psychology, Central Forensic Science Laboratory, CBI, Delhi 8. Dr. Lav Kesharwani (Asst.Prof.) School of Forensic Science, Sam Higginbottom Institute of Agriculture Technology & Sciences, Allahabad U.P, 9. Dr. Anu Sharma (Associate Prof) Dept of Anatomy, DMCH, Ludhiana (PB) 10. Dr. Shalini Gupta (Prof) Oral Pathology and Microbiology, Dental Sciences King George Medical University, Lucknow, UP 11. Dr Rituja Sharma, Associate Prof, Law Banasthali Vidyapeeth Jaipur NATIONAL EDITORIAL ADVISORY BOARD Chairman Prof Sudhir K Gupta - Head, Department of Forensic Medicine All India Institute of Medical Sciences, New Delhi Members 1. Prof. SK Dhattarwal, Forensic Medicine, PGIMS, Rohtak,Haryana 2. Prof. N K Aggrawal Forensic Medicine, UCMS, Delhi 3. Prof Ajay Ghangale Forensic Medicine Dr DY Patil Medical College, Pune, Maharashtra 4. Dr. Amar Jyoti Patwory Professor, Forensic Medicine NEIGRIHMS, Shillong 5. Dr S. Venkata Raghava Professor, Forensic Medicine, Banglore Medical College, Bengaluru 6. Prof Praveen Arora, Professor Department of Forensic Medicine & Toxicology, SAIMS, Indore 7. Dr. Pankaj Datta (Principal & Head) Department of Prosthodontics, Indraprastha Dental College & Hospital, Ghaziabad 8. Dr. Mahindra Nagar (Head) Department of Anatomy, UCMS & GTB Hospital, Delhi 9. Dr. Virender Kumar Chhoker Professor Forensic Medicine and Toxicology, Santosh Medical College, Ghaziabad, UP 10. Dr. Dayanand G Gannur (Professor) Department of Forensic Medicine & Toxicology, Shri BM Patil Medical College, Hospital & Research centre, Bijapur, Karnataka 11. Dr. Alok Kumar Professor Department of Forensic Medicine & Toxicology, UP Rural Institute of Medical Sciences and Research, Saifai, Etawah, U.P. Print-ISSN:0973-9122 Electronic - ISSn: 0973-9130 Frequency: Quarterly, Website: www.ijfmt.com Editor Dr. R.K. Sharma Institute of Medico-legal Publications Logix Office Tower, Unit No. 1704, Logix City Centre Mall, Sector- 32, Noida - 201 301 (Uttar Pradesh) Printed,

published and owned by Dr. R.K. Sharma Institute of Medico-legal Publications Logix Office Tower, Unit No. 1704, Logix City Centre Mall, "Indian Journal of Forensic Medicine & Toxicology" is peer reviewed Sector- 32, Noida - 201 301 (Uttar Pradesh) quarterly journal. It deals with Forensic Medicine, Forensic Science, Toxicology, DNA fingerprinting, sexual medicine and environment medicine. It has been assigned International standard serial No. p-0973-9122 and e- 0973-9130. The Journal has been assigned RNI Published at No. DELENG/2008/21789. The journal is indexed with Index Copernicus (Poland) and is Institute of Medico-legal Publications covered by EMBASE (Excerpta Medica Database). The journal is also abstracted in Chemical Abstracts (CAS) database (USA. The journal is also covered by EBSCO (USA) database. Logix Office Tower, Unit No. 1704, Logix City Centre Mall, The Journal is now part of UGC, DST and CSIR Consortia. It is now offical publication of Sector- 32, Noida - 201 301 (Uttar Pradesh) Indian Association of Medico-Legal Experts (Regd.). 1712 Indian Journal of Forensic Medicine & Toxicology, October-December 2019, DVOoIl. N13u,mNboe.r4: 10.5958/0973-9130.2019.00555.3 The Effect of Ethanol Extract Black Cumin (Nigella sativa) on Renal ET-1 and eNOS Expression Mice Preeclampsia Model Titi Maharrani1, Sanarto Santoso2, I Wayan Agung Indrawan3, Deasy Irawati1, Sukesi1 1Midwifery Department, Health Polytechnic of Surabaya, 2Microbiology Laboratory, Faculty of Medicine, Brawijaya University, 3Obstetrics and Gynecology Department, Saiful Anwar Hospital, Malang Abstract Objective: to determine the effect of Nigella sativa ethanol extract on serum sFlt-1 levels and expression of renal ET-1 mice model of preeclampsia. Method: This research was a laboratory experimental research with post test only control group design. This study used 30 BALB / C mice which were divided into 6 groups, namely negative control which was pregnant mice injected with serum of normal pregnant women, positive control was preeclampsia model mice, and treatment groups 1, 2, 3 and 4 were mouse models of preeclampsia get 500 mg, 1000 mg, 1500mg and 2000mg / kgBB / day ethanol extract of Nigella sativa for 5 days. Statistical analysis using ANOVA. Results: Mean renal ET -1 expression in mice preeclampsia model in treatment groups were 500mg, 1000mg, 1500mg and 2000mg (9.6+1.8%, 6.8+1.3%, 4.6+1.5% dan 5.4+1.5%) showed significant differences (p <0.05) and found a decrease in renal ET -1 expression with increasing dose. Same like that, mean expression of eNOS kidney showed significant differences in the treatment group dose 500mg, 1000mg, 1500mg and 2000mg (56 .3± 3 .2%, 63.8±3.3%, 78.0±5.4%, 66.9±1.9%). Conclusion: The administration of ethanol extract of black cumin seeds (Nigella sativa) decrease renal ET-1 expression and increase renal eNOS expression mice preeclampsia model and the effect was dose dependent. Keywords: Endothelin -1, eNOS, Nigella sativa, preeclampsia Introduction Preeclampsia is one of the complications in pregnancy(1) that causes the most maternal death after haemorhagic post partum2. WHO states that at least 16% of maternal deaths in developing countries caused by hypertension in pregnancy, especially eclampsia(2), where the incidence of preeclampsia occurs in 2-8% among all pregnancies(3). In East Java, preeclampsia/ eclampsia are the main cause of maternal death (34.88%) followed by haemorhagic (25.09%) in the second position(4). In normal pregnancy there is artery spiralis remodeling, trophoblast invasion into the lining of the artery spiralis muscle and surrounding tissue which Corresponding author: Titi Maharrani E-mail: titimaharrani@gmail.com Address: Karangmenjangan Street, Surabaya, Indonesia results in the tissue becoming softer and facilitating the spiral arteries to dilate so that blood flow in utero placenta increases. Whereas in preeclampsia failure of spiral artery remodeling results in decreased utero placental blood flow and placental hypoxia and ischemia(5). The presence of placental hypoxia will increase the production of Reactive Oxygen Species (ROS)(6), which will activate Hypoxia Inducible Factor α (HIF-1 α)(7) to stimulate the placenta to start

producing antiangiogenic factors, soluble endoglin (sEng) and soluble fms-like tyrosine kinase-1 (sFlt-1) which has an important role in the pathogenesis of preeclampsia(8). In preeclampsia there is an increase in antiangiogenic serum levels of sFlt-1(9) and is associated with the severity of preeclampsia(10). The high serum levels of sFlt-1 prevent the interaction between VEGF and PlGF angiogenic proteins with their receptors on the cell surface (flt-1 and flk-1) so decreased free VEGF and PlGF levels(9). Increased levels of sFlt-1 and decreased VEGF cause endothelial dysfunction and induce expression of endothelin-1 (ET-1) and decrease Nitric Oxide (NO(11). Indian Journal of Forensic Medicine & Toxicology, October-December 2019, Vol. 13, No. 4 1713 Vascular Endothelial Growth Factor (VEGF) will produce endothelial nitric oxide synthase (eNOS) through VEGFR-2 (KDR / Flk-1) which activates phosphoinositide 3-kinase (P13K) and anti apoptotic kinase / protein kinase B (Akt / PKB). Experimental study in preeclamptic mice show that lowering level VEGF will reduce the activation and expression of eNOS(7). eNOS is the main isoform that has a role in maintaining vascular tone through NO synthesis which is needed in maintaining vasodilation of kidney vessels. Black cumin seeds (Nigella sativa) have been widely studied and reported to have a number of uses including antioxidants and anti-inflammatory. Most of the therapeutic potential is due to the presence of thymoquinone (TQ) as the main active chemical component of this material(12). The role of black cumin seeds (Nigella sativa) as an antioxidant as a radical scavenger of various free radical agents(13). As an anti-inflammatory, TQ can inhibit production proinflammatory cytokines and transcription factors Nuclear Factor Kappa Beta (NFκβ)(12). This research was conducted to prove whether ethanol extract of black cumin seeds (Nigella sativa) can reduce expression ET-1 and incerase the expression of eNOS kidney mice model of preeclampsia. Method The research design used was a laboratory experimental research with post test only controlled group design research. This research was conducted in vivo in mice (Mus musculus). The research sample is 30 pregnant mice BALB/C were divided into six groups, each group contains 5 samples. One group pregnant mice injected with the serum of normal pregnant women were used as negative controls, one group mice preelampsia model as a positive control, and 4 groups of mice preeclampsia model receiving treatment Nigella sativa extract with dose 500 mg, 1000 mg, 1500 mg and 2000 mg/kg body weight/ day for 5 days. Mice preeclampsia model made by injecting severe serum preeclampsia pregnant women on day 10 and 11 gestation as much as 0.1 cc intraperitoneally(14),(15) The manifestation of preeclampsia in mice was found by finding hypertension and proteinuria on day 15 of gestation. Mice kept in the Pharmacology Laboratory of the Medical Faculty of Brawijaya University and get standart food and drink. This study was approved by the Ethics Committee of the Faculty of Medicine, Brawijaya University. Mice are terminated at 20 weeks gestation then their kidney were taken. Measurement of renal ET-1 and eNOS expression was carried out using IHC method using ET-1 merck Abcam antibody with Biocare Medical brand CPI kit then visually observed ET-1 protein expressed in experimental animal kidney tissue, using Olympus enlargement photo dot slide software 400 times. From each slide, 5 fields of view were taken, the average of each preparation was made in percent. Visual observation of eNOS enzymes expressed in glomerular endhotel cells in kidney tissue of mice, using photo dot slide olympus software, 20 visual fields, magnification 1000 times, postive eNOS if there is brown colour in the tissue. Percentage of eNOS = cells (+ eNOS)/gamma cells x 100%. Findings The results showed that there were significant difference (p = 0. 000) mean of expression of renal ET-1 between negative (healthy) control group (2.8+0.8%) with positive control group (mouse preeclampsia model) (13+1.6%). Similarly there were significant difference (p=0.000<) mean of expression renal eNOS between negative control group (healthy mice) (85.74±5.75%) with

positive control group (mice preeclampsia model) (42.3±4.13%). Table 1. Renal ET-1 and eNOS expression in the positive and negative control group Variable Negative control (healthy) Mean±SD Positive control Mean±SD p-value ET-1 expression (%) 2.8+0.8 13+1.6 0.000 eNOS expression (%) 85.74±5.75 42.3±4.13 0.000 Note: If the p-value <∝ = 0.05 means that there are significant differences and if p-value > 0.05 means there is no significant difference. 1714 Indian Journal of Forensic Medicine & Toxicology, October-December 2019, Vol. 13, No. 4 Based on the results of the one way Anova test on renal ET-1 expression data obtained a significant difference of five observation sample groups (p-value = 0.000). Then in Multiple Comparisons with the Least Significant Difference (LSD) test showed that there was a significant difference in mean renal ET-1 expression between the positive control group (mice preeclampsia model) (13 + 1.6%) with the treatment group administered Nigella sativa ethanol extract with dose 500mg (9.6 + 1.8%), with a dose of 1000mg (6.8+1.3%), with a dose of 1500mg (4.6+1.5%), and also with a dose of 2000mg (5.4+1.5%). This means that there is an effect of treatment with 500 mg, 1000 mg, 1500 mg, and 2000 mg of ethanol extract of Nigella sativa on the renal ET-1 expression in mice preeclampsia model. The Result of Anova one way test in kidney eNOS expression shows meaningful difference in fifth kidney of observation sample group (score p-value = 0.000). Based on the result of double comparison test by using LSD method shows that there is meaningful difference of average expression preeclamptic mice kidney eNOS model (42.3±4.1a%) with group that given ethanol extract of Nigella sativa 500mgs, 1000 mgs, 1500 mgs and 2000 mgs dosage (56.3±3.2b %, 63.8±3.3c %,78.0±5.4d % dan 66.9±1.9c %). It seems there is an enhancement of kidney eNOS expression during increasing dosage of Nigella sativa ethanol extract which has given to the preeclamptic mice model, but there is decrease in 2000mgs dosage group. Among those 3 dosage, 1500mgs dosage shows the biggest kidney eNOS expression. Therefore, 1500mgs dosage admitted as the faster to enhance mice preeclamptia model renal eNOS expression. There was decrease in renal ET-1 expression along with the increase in doses of ethanol extract of Nigella sativa black cumin seeds against preeclampsia mice, except at a dose of 2000 mg increased slightly. Therefore a dose of 1500 mg can be considered to be the fastest increase in the diameter of the renal arterioles in mice preeclampsia model. Mean renal ET-1 expression (panel A) and renal eNOS expression (panel B) in negative control (healthy mice), positive control (preeclampsia model mice), and 4 groups of preeclamptic models of mice and Nigella sativa ethanol extract with dose of 500 mg, 1000 mg, 1500 mg, and 2000 mg. There is a decrease in renal ET-1 expression and increase in renal eNOS expression as dose increases. A dose of 1500 mg seems to be the optimal dose of lowering renal ET-1 expression (panel A) and increase renal eNOS expression in mice preeclampsia model. Figure 1. Comparison of ET-1 expression in glomerular endothelial cells Comparison of ET-1 expression in each treatment group. (A) negative control group; (B) positive control group; (C) treatment group I; (D) treatment group II; (E) III treatment group; (F) IV treatment group. The most ET-1 expression was seen in the positive control group marked with brown color. Discussion This study showed eNOS expression in glomerular endothelial cells in preeclampsia mice modeled on serum PEB pregnant women proved to have a meaningful decline compared to control mice (p-value = 0.000 <). Increased production of ROS (ONOO-, O2- and H2O2) seems to suppress expression and function of eNOS. Increased ROS can cause low L-Arg substrate concentration or oxidicide cofactor tetrahydrobiopterin (BH4). This causes eNOS not only synthesize NO but also superoxide free radicals (O2-). O2- has an effect on endothelial cell damage and reacts with NO to produce peroxinitrite(17). The decrease of eNOS expression in this study suspect by effect of PEB maternal serum injections in pregnant mice causing

hypoxia of mice's placenta. Placenta hypoxia will increase ROS production and activate several transcription factors including Nuclear Factor Kappa Beta (NFκβ), Protein-1 Activator (AP- 1), and Hypoxia-Inducible Factor-1 (HIF-1). Placenta hypoxia is also possible directly can decreases the activation of eNOS. The decrease of eNOS can causes decreasing bioavibility of NO and increase blood pressure. Based on the results of the one way Anova test, there are significant different (p-value <0.05) renal eNOS Indian Journal of Forensic Medicine & Toxicology, October-December 2019, Vol. 13, No. 4 1715 expression between mice preeclampsia model (positive control) with treatment groups which is get ethanol extract of black cumin at dose 500 mg, 1000 mg, 1500 mg, and 2000 mg. Khodja & Kerth (2012) study also reported that adult mouse which get 10 mg/kg/day TQ in their drink for 14 days had increase eNOS expression in mesenkim artery. Lowering eNOS expression in mice preeclampsia model suspected to be due the role of NS as an antioxidant. But the mechanism is not fully understood. The ability of TQ and dythimoquinone which is an active substance in NS has a role as a radical scavenger suspected to be a contributing factor. Free electrons found in antioxidants will bind ROS which is a hyperactive molecule that results from the reduction of oxygen molecules. Thus, ROS production will decrease and then followed by lowering eNOS expression. This study showed an increase in renal eNOS expression along with increasing doses of black cumin ethanol extract (Nigella sativa), and dose 1500 mg NS is the optimal dose to increase renal eNOS expression. However, at dose 2000 mg NS there was decrease even though it was not significant. The study found that the administration of exogenous antioxidants in excessive amounts can have detrimental effect as pro-oxidants.(15) The excessive content of the active ingredient in black cumin ethanol extract (Nigella sativa) at dose of 2000 mg thought have pro-oxidant effect, which can cause cell damage and tissue function due to lipid peroxide, modified proteins and amino acids, and DNA oxidation. Therefore giving antioxidants must be sufficient to maintain balance of pro-oxidants and antioxidants. This study also reported that there were significant differences between the mean renal Endothelin 1 (ET-1) expression in mice preeclampsia model (positive control) (12.80 + 1.6) with the treatment group of ethanol extract of black cumin seeds (Nigella sativa) dose of 500 mg. day, 1000 mg/ kg /day, 1500 mg/ kg /day and 2000 mg/ kg/ day with a p-value of 0.000 (p <0.05). This proves that administration of ethanol extract of black cumin seeds (Nigella sativa) can reduce renal ET-1 expression at mice preeclampsia model. These results are in line with in vivo research conducted by Mazouchian et al. (2013) of 40 pigs made asthma and given TQ in low and high doses. From the study, the results of ET-1 levels in lung tissue in the group given TQ in low doses (20 μM) were lower compared to controls. This explains that TQ, the main ingredient of black cumin seeds (Nigella sativa) can reduce ET-1 levels. Other studies also reported that the administration of black cumin seed extract (Nigella sativa) can significantly reduce blood pressure.(22),(23) The mechanism of decreasing ET-1 by black cumin seed extract (Nigella sativa) is also through its potential as an antioxidant that has been tested to be able to fight several reactive oxygen species (ROS). The existence of this ability will suppress the formation of peroxynitrit (ONOO-) which in turn will reduce the occurrence of endothelial dysfunction which is characterized by a decrease in ET-1 which in turn will cause smooth muscle relaxation which will reduce blood pressure(13). In line with renal eNOS expression, the least expressed expression of ET-1 kidney in treatment group 3 was given ethanol extract of black cumin seeds (Nigella sativa) 1500 mg/KgBW/day. Whereas in the treatment group 4 which was given ethanol extract of black cumin seeds (Nigella sativa) 2000 mg/KgBW/day experienced a slight increase in ET-1 expression compared to treatment group 3. This was due to the hormesis effect of giving black cumin seed extract (Nigella sativa)(24). Conflict of Interest: No Source of Funding: Authors Ethical Clearance: Yes

References 1. George EM, Granger JP. Endothelin: key mediator of hypertension in preeclampsia. Am J Hypertens. 2011;24(9):964-969. doi:10.1038/ajh.2011.99. 2. Khan KS, Wojdyla D, Say L, Gülmezoglu a. M, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367:1066- 1074. doi:10.1016/S0140-6736(06)68397-9. 3. Ghulmiyyah L, Sibai B. Maternal Mortality From Preeclampsia/Eclampsia. Semin Perinatol. 2012;36(1):56-59. doi:10.1053/j. semperi.2011.09.011. 4. Health Office of East Java province. Health Profile of East Java in 2012. Surabaya: Health Office of East Java province; 2013. 5. George EM, Colson D, Dixon J, Palei AC, Granger JP. Heme oxygenase-1 attenuates hypoxia-induced sFlt-1 and oxidative stress in placental villi through 1716 Indian Journal of Forensic Medicine & Toxicology, October-December 2019, Vol. 13, No. 4 its metabolic products CO and bilirubin. Int J Hypertens. 2012;2012. doi:10.1155/2012/486053. 6. Herrera E a., Krause B, Ebensperger G, et al. The placental pursuit for an adequate oxidant balance between the mother and the fetus. Front Pharmacol. 2014;5 JUN(June):1-10. doi:10.3389/ fphar.2014.00149. 7. Semenza GL. REVIEWS Regulation of Oxygen Homeostasis by. 2009. 8. Kanasaki K, Kalluri R. The Biology of Preeclampsia. Kidney Int. 2009;76(8):831-837. doi:10.1016/j. biotechadv.2011.08.021.Secreted. 9. Maynard SE, Min J, Merchan J, et al. Excess Placental Soluble fms-like Hypertension , and Proteinuria in. 2003;58(5):564-581. doi:10.1172/ JCI200317189.Introduction 10. Shibuya M. Vascular endothelial growth factor and its receptor system: Physiological functions in angiogenesis and pathological roles in various diseases. J Biochem. 2013;153(1):13-19. doi:10.1093/jb/mvs136. 11. Yi KW, Jung SH, Cho GJ, et al. Effects of sFlt-1 and alpha 2-macroglobulin on vascular endothelial growth factor-induced endothelin-1 upregulation in human microvascular endothelial cells. Placenta. 2014;35:64-69. doi:10.1016/j. placenta.2013.09.008. 12. Ahmad A, Husain A, Mujeeb M, et al. A review on therapeutic potential of Nigella sativa: A miracle herb. Asian Pac J Trop Biomed. 2013;3(5):337- 352. doi:10.1016/S2221-1691(13)60075-1. 13. Leong X, Mustafa MR, Jaarin K. Nigella sativa and Its Protective Role in Oxidative Stress and Hypertension. 2013;2013. 14. Kalkunte S, Boij R, Norris W, et al. Sera from preeclampsia patients elicit symptoms of human disease in mice and provide a basis for an in vitro predictive assay. Am J Pathol. 2010;177(5):2387- 2398. doi:10.2353/ajpath.2010.100475. 15. Wicaksono BA, Candra S, Baktiyani W, Fitri LE. Intraperitoneal Injection of High Tumor Necrosis Factor (TNF-α) Serum Increase Soluble Fms-like Tyrosine Kinase 1 (sFlt-1) and Blood Pressure of Pregnant Mice. J Trop Life Sci. 2015;5(1). 16. Foster RR. The Importance of Cellular VEGF Bioactivity in the Development of Glomerular Disease. Nephron Exp Nephrol. 2009;113(1):e8- e15. doi:10.1159/000228078. 17. Chen Y. Novel Angiogenic Factors for Predicting Preeclampsia: sFlt-1, PlGF, and Soluble Endoglin~ ! 2 0 0 8 - 0 8 - 2 9 ~ ! 2 0 0 8 - 1 2 - 1 5 ~ ! 2 0 0 9 - 0 1 - 0 2 ~ ! Open Clin Chem J. 2009;2(1):1-6. doi:10.2174/ 1874241600902010001. 18. Wang A, Rana S, Karumanchi SA. Preeclampsia: the role of angiogenic factors in its pathogenesis. Physiology (Bethesda). 2009;24:147-158. doi:10.1152/physiol.00043.2008. 19. Zhou CC, Irani R a, Dai Y, et al. Autoantibody- mediated IL-6-dependent endothelin-1 elevation underlies pathogenesis in a mouse model of preeclampsia. J Immunol. 2011;186(10):6024- 6034. doi:10.4049/jimmunol.1004026. 20. Poston L, Igosheva N, Mistry HD, et al. Role of oxidative stress and antioxidant supplementation in pregnancy. Am J Clin Nutr. 2011;94:1980-1985. doi:10.3945/ajcn.110.001156.1. 21. Mansour MA, Nagi MN, El-khatib AS, Al-bekairi AM. Effects of thymoquinone on antioxidant enzyme activities , lipid peroxidation and DT- diaphorase in different tissues of mice : a possible mechanism of action. Cell Biochem Funct. 2002;20(October 2001):143-151. 22. Dehkordi. FR KA. Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension. Fundam Clin

Pharmacol. 2008;4:447-52. 23. Najmi A, Nasiruddin M, Khan RA, Haque SF. Indigenous herbal product Nigella sativa proved effective as an antihypertensive in metabolic syndrome. Asian J Pharm Clin Res. 2013;6(1):61- 64. 24. Mattson MP. Hormesis defined. Ageing Res Rev. 2008;7(1):1-7. doi:10.1016/j.arr.2007.08.007. 25. Bouayed J, Bohn T. Exogenous antioxidants— Double-edged swords in cellular redox state. 2010;3(4):228-237. doi:10.4161/oxim.3.4.12858.